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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Subject: **Docket No. 2005D-0122**
Draft Guidance for Industry, Investigators, and Reviewers: Exploratory IND Studies

Dear Sir/Madam:
Amgen is a global biotechnology and pharmaceuticals products company based in Thousand Oaks, California. We appreciate the work FDA is doing with regard to the Critical Path Initiative and, as such, are pleased to provide the following comments on the draft guidance, *Exploratory IND Studies:*

General Comments:

(1) The first sentence of the draft guidance (lines 21 to 24) makes reference to therapeutic biological products. However, most of the information on toxicity testing appears to be specific to small molecules. We recommend that additional detail be added to the document to clarify which sections are relevant only to small molecules. In sections that are relevant to biologic products, we suggest that the guidance provide greater clarity regarding the studies required to support the various examples of exploratory INDs.

(2) The term "*closely related drugs*" (line 23) should be better defined. For small molecules this appears to include different salts/esters of an active agent as well as closely related active moieties. In particular, closely related active moieties should be better defined because small changes in structure may have dramatic effects on toxicity endpoints. In addition, "relatedness" of active moieties can be a subjective assessment.

(3) We agree that the preclinical requirements to support a microdose study offer efficiencies when compared with the preclinical requirements to support a traditional IND, as described in the ICH M3 guidance. However, it is not clear that the preclinical requirements described in the draft guidance to support other types of exploratory INDs would significantly expedite the early drug development process.

(4) This guidance should reference the FDA's guideline on single-dose acute toxicity testing, which describes the FDA's acceptance of single-dose toxicity studies in support of single-dose clinical trials as an additional alternative to expedite early drug development (*Guidance for Industry: Single Dose Acute Toxicity Testing for Pharmaceuticals*).

(5) Allowance for a third, "middle ground" type of exploratory IND would be useful. Currently, the two most defined examples are a microdose study (1/100th of the calculated pharmacologically effective dose or < 100 micrograms) and a "pharmacological effect" study lasting up to 7 days. The limitation with these choices is that doses of < 100 micrograms can sometimes not properly assess the PK of a drug given at larger, pharmacologically relevant doses, and this cannot always be determined a priori. Some blend of the 2 proposals could, therefore, be very useful—for example, a hybrid in which a single-dose NOAEL is established in a manner similar to that described for the "pharmacological effect" study. This would permit doses as described in lines 379 to 386, but limited to a single dose in humans. Since it would be limited to a single dose, the other toxicity studies potentially would not be necessary. Even if a repeated-dose toxicity study were deemed necessary, other testing might not be required as long as the human trial was limited to a single dose.

In Section III.C.2, the wording in the description for the "pharmacological effect" study seems to generally assume a multiple-dose study. However, the wording in other parts of the document seems to provide sufficient flexibility that a higher dose PK study may be possible within the stated parameters. It might be helpful to re-title this section to: *Clinical trials to study pharmacologically relevant doses.*

Specific Recommendations:

(1) Footnote 9 should be clarified, as it is not absolutely clear if the footnote is intended to describe studies done under CFR 361.1. Not all the conditions of 361.1 are included in the footnote, and the situation cited, ie, "*following the initial publication in the medical literature of a first in human experience with that radiolabeled compound*" is just one possibility. Proposed revised text for Footnote 9: *A radiolabeled candidate compound can be administered at doses that are known to have no pharmacologic effect in humans without an IND application in basic research studies carried out under 21 CFR 361.1.*

(2) Line 240: Is the term "*active substance*" synonymous in this context with "*drug substance*"?

(3) Line 286: This line states that the impurity profile should be characterized. We recommend that guidance should be provided regarding the acceptable and unacceptable differences in the profiles.

(4) Lines 310 to 311: The scientific rationale for the 100-μg dose limit in microdose studies should be referenced. If the 100-μg limit cannot be supported by scientific evidence, then we suggest that a limit dose that can be supported by scientific data should be established.

(5) Lines 317 to 328: Please clarify whether single-dose toxicity studies supporting microdose clinical trials would require the use of both sexes.

(6) Lines 342 to 343: The guidance states that the clinical trial can be supported by a 2-week repeated-dose toxicology study in a sensitive species accompanied by toxicokinetic evaluations. We assume that for a biologic product, a 2-week study in the appropriate non-human primate species would support the clinical trial, and that a confirmatory study in a second species would not be required. The guidance should state specifically the requirements for biologic products.

(7) Lines 345 to 347: With regard to the choice of species for the repeated-dose toxicity study, the current wording could be construed to mean that if a non-rodent species is used

for the initial study to establish a NOAEL, then only that one species is necessary. However, the flow diagram does not support this, so clarification is needed.

(8) Lines 351 to 353: Regarding the choice of a single dose to be used in the confirmatory study (approximating the rat NOAEL calculated on the basis of body surface area): please confirm that this is based entirely on dose, and not on exposure.

(9) Lines 356 to 358: The guidance states that the number of repeated doses in the toxicity study in a second species should, at a minimum, be equal to the number administrations intended clinically. Could a single-dose toxicity study, therefore, support a single-dose clinical trial?

(10) Lines 366 to 367: Are safety pharmacology studies not required if pharmacological effects are not being explored (or expected)? This suggests the possibility of a PK study at more pharmacologically relevant doses as described in General Comment No. 5 (above).

(11) Lines 367 to 370: We suggest the following addition to this sentence: *Evaluation of the central nervous and respiratory systems can be performed as part of the rodent toxicology studies, while safety pharmacology for the cardiovascular system can be assessed in the nonrodent species, generally the dog,* ***and can be conducted as part of the confirmatory or dose-escalation study.***

(12) Lines 372 to 377: The criteria that would necessitate genotoxicity assessment should be specified. If a single-dose trial (to assess PK at doses > 100 micrograms) is planned, would genotoxicity testing still be necessary? The guidance should state that genotoxicity tests are not required for biologic products and reference ICH S6.

(13) Footnote 18: The guidance referenced in this footnote appears to be the incorrect guidance. We believe guidances S2A: *Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals* and *S2B: Genotoxicity: A Standard Battery for Genotoxicity Testing for Pharmaceuticals* should be referenced instead.

(14) Lines 372 to 377: This paragraph should be clarified with regard to the need for an in vivo chromosomal aberration assay. Line 375 appears to state that an in vitro chromosomal aberration assay would be sufficient and that an in vivo assay is optional. Is this interpretation accurate? In addition, we suggest that you clarify that the in vivo assay could be a micronucleus assay.

(15) Line 382: Please clarify if criterion 1 (1/4 of the 2-week NOAEL) should be based on the calculated mg/m^2 dose value. In addition, this line refers to a 2-week rodent toxicity study. Is it possible that a single-dose study would suffice (see Specific Comment no. 9 above)?

(16) Lines 382 to 383: Criterion 2 should be reworded for clarity: "*...1/2 of the AUC at the NOAEL in the 2-week rodent study, or* ***1/2 of*** *the AUC in the dog at the rat NOAEL....*" Again, it should be clarified whether this would be the rat NOAEL expressed as a mg/kg dose, or the dog equivalent of the rat NOAEL based on a mg/m^2 conversion.

(17) Lines 388 to 424:

(a) The discussion of clinical trials to evaluate mechanism of action is vague. It is unclear how these trials differ from those discussed in the previous section (clinical trials to study pharmacological effects).

(b) The nature of the preclinical studies that would support initiation of clinical MOA trials is unclear. We suggest that this section state explicitly what preclinical toxicity studies would be required.

(18) Attachment (lines 445-455):

(a) The required genotoxicity tests should be more consistent with section IIIC2 and specified more clearly, ie, the bacterial mutation assay should be listed as well as the option to conduct either an in vitro or in vivo chromosomal aberration assay.

(b) NOAEL units should be specified (AUC, mg/kg, or mg/m^2). The third criterion for calculation of the clinical stop dose should be reworded for clarity: "*Clinical equivalent of 1/2 of rat or nonrodent AUC at the rat NOAEL – whichever is lower*"

(c) The flow diagram should reflect more of the flexibility described in the text. For example, the diagram assumes a 2-week study. If, on the other hand, the attachment is intended to be just one representative example, perhaps it could be more clearly labeled as such: ***One Example*** *of a Preclinical Toxicology Testing Strategy For Exploratory INDs Designed To Administer Pharmacologically Active Doses.*

(19) Lines 417 to 424: The discussion of GLP status should be moved to the beginning of Section C (possibly to Line 307). In its current location, it appears to pertain only to studies supporting MOA trials.

If you have any questions regarding our comments, or how we may assist with further development of this guidance, please contact Jenny Peters at 805-447-8840.

Sincerely,

Jenny Peters
Amgen Regulatory Affairs